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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/791,618	03/02/2004	Sherman Fong	P1192-2C1	4005

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EXAMINER	
DEBERRY, REGINA M	

ART UNIT	PAPER NUMBER
1647	

MAIL DATE	DELIVERY MODE
03/31/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/791,618	FONG ET AL.	
	Examiner	Art Unit	
	REGINA M. DEBERRY	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

In view of the Appeal Brief filed on 13 November 2007, PROSECUTION IS HEREBY REOPENED. A new ground of rejection is set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below:

Status of Application, Amendments and/or Claims

Claims 12-14 are pending and under examination.

Withdrawn Objections And/Or Rejections

The rejection to claims 12-14 under 35 U.S.C. 101, as set forth at pages 3-9 of the previous Office Action (16 January 2007), is *withdrawn* in view of art which establishes the mixed lymphocyte reaction (MLR) assay as an art accepted assay for identifying immune suppressive molecules and is generally predictive of their *in vivo* effectiveness.

Claim Rejections - 35 USC § 112, First Paragraph, Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are drawn to methods of enhancing the infiltration of immune cells in a mammal, comprising administering to said mammal an effective amount of Bolekine polypeptide (SEQ ID NO:2) and a method of alleviating infection in a mammal comprising administering an effective amount of Bolekine polypeptide (SEQ ID NO:2). Example 10 states that the polypeptides of the invention are active as stimulators of the proliferation of T-lymphocytes. Compounds which stimulate proliferation of lymphocytes are useful therapeutically where an enhancement of an immune response is beneficial.

Example 10 teaches the stimulatory activity of the Bolekine polypeptide (SEQ ID NO:2) in a mixed lymphocyte reaction (MLR). Bolekine at a concentration of 12.40 nM had a 112% increase over the control. Bolekine at a concentration of 124.00 nM had a 192.7 % increase over the control (Table 7). Example 11 states that Bolekine stimulates an immune response and can induce inflammation by inducing mononuclear cells, eosinophils and PMN infiltration at the site of injection of the animal in the vascular permeability assay. Example 11 states that sites with visible inflammatory cell inflammation are scored as positive. Inflammatory cells may be neutrophilic, eosinophilic, monocytic or lymphocytic. Example 11 states that at least a minimal perivascular infiltrate at the injection site is scored as positive and that Bolekine scored positive (pages 87-88).

Because the MLR assay is an accepted *in vitro* model for screening immunosuppressive agents for use in the prevention of graft-versus-host disease and graft rejection, the assay must be evaluated as it pertains to the asserted use of the instant invention, which is for therapeutically enhancing the infiltration of immune cells and alleviating infection in a mammal. It is unclear *how the results of the MLR assay relate* to the claimed invention. Haskill et al., US Patent No. 5,817,306 teach that the MLR assay is valuable for identifying immune suppressive molecules *in vitro* that are useful for treating graft versus host disease (column 12, lines 36-41). Coleman et al., US Patent No. 5,780,268 teach that investigation of MLR assays have provided information on graft rejection and its suppression and contributed to the understanding of the multiplicity of phenotypes that are important in histocompatibility. The Miles

Assay may be used to investigate the properties of substances that increase permeability. Miles et al. (reference of record) teach that in animals with a recently injected vital dye in their blood, the intradermal injection of substances that increase permeability of the blood vessels is followed by an accumulation of dye at the site of injection, presumably due to the passage of an excess of dye-stained plasma into the tissue spaces. When the blood flow and the vascular bed of the skin are relatively constant, differences in the size and intensity of stained areas of skin reflect differences in vascular permeability, and may be used to investigate the properties of substances that increase permeability in this way. *However,* basic irritants such as lye would test positive in the Miles assay. In the absence of further characterization of what type of reaction the substance causes and what the system effects of such are, the results in the Miles assay are preliminary, necessitating further research. In addition, Yeo et al. (reference of record) teach that the Miles assay has been used widely to detect vascular permeability factor (VPF) in culture medium of tumor cells as well as in tumor ascites fluid. Yeo et al. teach that this assay is not specific because it will detect permeability changes in response to other inflammatory mediators besides VPF. Yeo et al. teach that fluids from different animal species cannot be used because foreign proteins commonly elicit nonspecific permeability changes, leading to a false-positive Miles test.

The ability to stimulate lymphocyte Bolekine proliferation in the MLR assay (an *in vitro* model for screening immunosuppressive agents) and cause inflammation at the site of injection in a vascular permeability assay (an *in vitro* model for preliminary screens of potential proinflammatory molecules) is not tantamount to an effective

method of enhancing the infiltration of (any type of) immune cells (in any type of disease or condition) and/or alleviating any type of infection in a mammal. The assertion that the claimed invention could be useful for the treatment of conditions where the enhancement of the immune response would be beneficial encompasses many diverse conditions/diseases such as the common cold or HIV. The limitation "alleviating infection" encompasses STDs, tuberculosis, pink eye, bronchitis, bladder infections, etc. It is not predictable which disease/condition the claimed invention may function, if any. The data from the instant assays does not teach what specific setting, the claimed invention **would predictably function.** Therefore, while the art recognizes the instant assays as accepted screening methods, the Bolekine data does not correlate to use of the claimed protein in a therapeutically effective manner for the breadth of the instant claims.

Due to the large quantity of experimentation necessary to determine how to use the claimed Bolekine polypeptide (SEQ ID NO:2) in an *in vivo* therapeutic effective manner to enhance the infiltration of ***any type*** of immune cell ***(in any type of disease/conditions***) and/or to ***alleviate any type of infection***, the lack of direction/guidance presented in the specification regarding same; the absence of working examples directed to same; the complex nature of the invention; the unpredictability of employing an *in vitro* immune assay to predict/correlate with *in vivo* immuno-efficacy of the instant polypeptide; and the breadth of the claims which fail to ***recite a specific condition/disease, wherein Bolekine enhances the infiltration of***

immune cells and alleviates infection, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

Applicants argue that Bolekine is a novel cytokine and its structure is consistent with the asserted utility. Applicant cites Baggiolini et al. (reference of record). Applicant argues that the MLR assay is a well established assay for evaluating test compounds, such as the Bolekine polypeptide, for their ability to stimulate T-lymphocyte proliferation *in vitro* and consequently for assessing the immune response of an individual. Applicant cites Current Protocols in Immunology (reference of record). Applicant argues that they rely on the identification of Bolekine as a novel cytokine, and data from the Mixed Lymphocyte (MLR) assay and the Vascular Permeability Assay. Applicant argues that Bolekine showed positive activity in the MLR assay and that two expert declarations under 37 CFR 1.132, confirm the validity of the experimental data provided in the specification. Applicant argues that the Fong Declaration (dated 6/16/04) provides clinical applications for immune stimulants which have been shown to stimulate T cell proliferation in the MLR assays, such as chemokine IL-12, used in the treatment of melanoma. Applicant argues that IL-12 is a known immune stimulant, which has been shown to stimulate T-cell proliferation in the MLR assay and was identified in an MLR assay. Applicant cites Gubler et al. (reference of record). Applicant argues that researchers have demonstrated the efficacy of the approach, relying on the immune stimulatory activity of IL-12 for the treatment of melanoma. Applicant cites Peterson et al. and Thurner et al. (reference of record). Applicant argues that the Fong Declaration (dated 8/27/04) provides a detailed explanation of the Vascular Permeability Assay. In

the declaration, Dr. Fong states that the Miles assay is well known in the art as an assay to identify proinflammatory molecules. Proinflammatory molecules can directly or indirectly cause vascular permeability by causing immune cells to exit from the blood stream and move to the site of injury or infection. The declaration states that these proinflammatory molecules recruit cells like leukocytes, which includes monocytes, macrophages, basophils, and eosinophils. These cells secrete a range of cytokines that further recruit and activate other inflammatory cells to the site of injury or infection. The declaration cites Hirahara et al. (reference of record) and states that the skin vascular permeability assay was used to determine if blood coagulation factor XIII (FXIII) could be used in treating Shonlein Henoch Purpura (SHP). The declaration cites Senger et al. (reference of record) and states that the Miles assay was used by to show that a secreted factor called vascular permeability factor (VPF) caused vascular permeability. The declaration states that Yeo et al. (1992, Clin. Chem. 38:71-75) confirmed the viability of the skin vascular permeability assay by correlating it with disassociation enhanced lanthanide fluoroimmunoassay (DELFIA) results.

Applicant's arguments have been fully considered but are not deemed persuasive. Even if, for arguments sake, the Bolekine protein were found to be a novel chemokine, it would not be enabled for the instant claims. Baggiolini et al. teach diverse functions for known chemokines and their effects on different types of leukocytes. Baggiolini et al. fail to teach that any one chemokine can enhance the infiltration of all immune cells (in any type of disease or condition) and/or alleviate any type of infection in a mammal. The Examiner cannot find in Current Protocols in Immunology a teaching

wherein a positive result in an MLR assay indicates that the protein can enhance the infiltration of any immune cells (in any disease/condition) and/or alleviate any type of infection *in vivo*. The Examiner cannot find in Current Protocols in Immunology a teaching wherein a positive result in an MLR assay indicates that the protein is identified as an immune stimulant that can be used *in vivo* to boost the immune system to respond to a particular antigen that may not have been immunologically active previously. Gubler et al. do not use the same MLR assay as disclosed in the instant specification. Gubler et al. use lymphoblasts, whereas the MLR assay uses dentritic cells. In addition, Gubler et al. also employed a Cr-release assay to discern cytotoxicity. Most importantly, Gubler et al. state that "the availability of the recombinant CLMF (IL-12) **will now make possible a broader and *more detailed characterization* of its biology** (last paragraph). Applicant argues that researchers have demonstrated the efficacy of the approach, relying on the immune stimulatory activity of IL-12, for the treatment of melanoma and cites Peterson et al. and Thurner et al. The Examiner does not doubt that immune stimulants find important **specific clinical applications**. Peterson et al. and Thurner et al. teach **IL-12 in a specific clinical application**; that which involves melanoma. Such **a specific clinical application** has not been taught by the instant disclosure for the Bolekine polypeptide.

The Miles assay is useful as a preliminary screen for potential proinflammatory molecules, but as was stated above, basic irritants, such as lye, would test positive in the Miles assay. Further work must be done subsequent to a positive result in a Miles assay to determine if and how a molecule may be used to alleviate infection. The

declaration refers to Hirahara et al., but is not sufficient to overcome the rejection. In the instant case, the claimed Bolekine protein tested positive in the assay. FXIII tested negative. Therefore, the results are not comparable. The declaration refers to Senger et al., but is not sufficient to overcome the rejection. Senger et al. set out to determine why vessels lining the peritoneal cavities of rodents with ascites tumors display markedly greater permeability than vessels in control animals and concludes that secretion of permeability-increasing activity appears to be a common feature of tumor cells and that VPR has permeability-increasing activity. Senger et al. do not suggest that VPR can be used to alleviate infection. Yeo et al. teach that VPF was first measured by using the Miles assay, which measures the extravasation of intravenously injected Evans Blue dye into the dermis of guinea pigs in response to intradermal injections of vascular permeability factor (VPF). Yeo et al. do not teach the Miles assay can be used to identify proinflammatory molecules that can be used to treat infection. Most importantly, Yeo et al. teach that the Miles assay is not specific because it will detect permeability changes in response to other inflammatory mediators besides VPF. Also, fluids from different animal species cannot be used because foreign proteins commonly elicit nonspecific permeability changes, leading to a false-positive Miles test. The state of the art shows that a positive result in the Miles assay is insufficient for the skilled artisan to conclude that a molecule can be used to alleviate infection *in vivo.* While particular irritants may have uses that stem from that irritant capability, in the absence of further characterization of what type of reaction the substance causes and what the systemic effects of such are, the result remains a preliminary one,

necessitating substantial further research to determine how to use the compound. It remains that the skin vascular permeability assay does not give sufficient information so as to inform one of skill in the art as to how to use the claimed polypeptide.

Applicant argues that at the effective filing date, one of ordinary skill would have understood which conditions benefit from the enhancement of the immune response. Applicant cited McElrath et al., McDyer et al., Zaki et al. and Tyring et al. (all references of record) and conditions such as HIV-1, cutaneous T cell lymphoma, viral infections and tuberculosis. Applicant argues that compounds that stimulate proliferation of lymphocytes in the MLR assay are useful therapeutically where enhancement of an immune response is beneficial.

Applicant's arguments have been fully considered but are not deemed persuasive. The Examiner understands that there are many conditions which benefit from an enhanced immune response; however, the results from the MLR assay and the Miles assay for the Bolekine protein are not applicable to the instant claims. The instant specification fails to teach a specific disease/condition, wherein an immune response can be enhanced or a specific type of infection which can be alleviated upon administration of the Bolekine protein. The references submitted by Applicant teach a specific disease, condition and/or infection (i.e. HIV, tuberculosis, cutaneous T cell lymphoma). It is not predictable of under what sort of situation (i.e. disease, condition) an immune response can be enhanced or what type of infection can be alleviated. Infections in diseases such as HIV and tuberculosis are complex. Cancer is another complex disease with diverse pathologies. It would be highly unpredictable to correlate

the data from an MLR and Miles assay with effectively administering the Bolekine protein to alleviate infection and enhance the infiltration of immune cells (in any condition/disease) in a mammal.

Applicant argues that the asserted utility of Bolekine is affirmed by post-published evidence. Applicant argues that Shurin et al. (reference of record) confirm the MLR results disclosed in the present invention by performing their own MLR assay and also finding that Bolekine (also known as CXCL14 or BRAK) is an immune cell chemoattractant). Applicant argues that Sleeman et al. (reference of record) found that CXCL14/BRAK/Bolekine was chemotactic for a B cell lymphoblastoid line and a monocytic cell and that the murine form of CXCL14/BRAK/Bolekine caused the migration of inflammatory cell *in vivo*.

Applicant's arguments have been fully considered but are not deemed persuasive. As was stated in the previous Office Action, (27 January 2006; page 4, 1st paragraph, lines 12-15), Applicant has not provided a sequence alignment, which demonstrates that the instant Bolekine polypeptide (SEQ ID NO:2) is indeed CXCL14/BRAK. Shurin et al. teach that BRAK is a new chemokine with unknown function and receptor selectivity. Shurin et al. teach that MLR assays were performed to evaluate the effect of BRAK on the ability of human dentritic cells (DC) to stimulate proliferation of allogenic T cells. Shurin et al. employ the use of SCID mice to demonstrate that BRAK is an inducer of immature DC migration. Sleeman et al. teach that the homology of KS1 to BRAK was 94% at the protein level, indicating KS1 as the murine homologue of the human BRAK gene. Sleeman et al. teach via an *in vivo* assay

(nude mice) that KS1 promotes the extravasation of cells other than T cells (B cells and monocytes). In summary, each reference discloses the migration of **specific cells**, not **any type of immune cells**, as recited in the instant claims. **Most importantly, the references fail to teach that BRAK or KS1, can be used to enhance the infiltration of (any type of) immune cells (in any type of disease/conditions) and/or alleviate any type of infection *in vivo*.** As was stated earlier, even if the Bolekine protein were found to be a novel chemokine, it would not be enabled for the breadth of the instant claims.

In conclusion, the submitted Declarations, the art of record and the instant specification fail to teach that the Bolekine polypeptide (SEQ ID NO:2) can act as an immunostimulant ***by any means***. The instant claims encompass administering Bolekine to infiltrate **any type of immune cells (in any type of disease/conditions) and/or alleviate any type of infection *in vivo*.** The specification fails to provide guidance or working examples, which correlate with the breadth of the instant claims. For these reasons, undue experimentation would be required to practice the claimed invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

RMD
3/24/08

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